New concepts in intracranial compliance: pathophysiology, monitoring and clinical implications

Sérgio Brasil[a], *Magdalena Kasprowicz*[b], *Mario Zaccarelli*[c] *and Laurent Gergele*[d]

Purpose of review
This review synthesizes recent advancements in understanding intracranial compliance (ICC) pathophysiology, explores novel monitoring techniques, and discusses their evolving clinical implications. We highlight how a shift from static intracranial pressure (ICP) thresholds to dynamic ICC assessment is transforming the management of acute brain injury.

Recent findings
ICC is the brain's ability to accommodate volume changes without significant ICP elevation, is a critical determinant of outcome in neurocritical care. The paradigm in ICC is evolving from a focus on absolute ICP values to a dynamic, continuous assessment of the brain's compensatory capacity. Emerging concepts extend the classical Monro-Kellie doctrine, incorporating the dynamic roles of cerebrospinal fluid circulation, including the glymphatic system, in maintaining intracranial homeostasis. Integrating new pathophysiological insights with advanced monitoring tools holds immense potential to refine clinical decision-making, enabling more proactive and personalized interventions, ultimately improving outcomes for patients with acute brain injury.

Summary
To achieve such goal, both invasive and noninvasive advanced monitoring techniques now provide real-time insights into ICC status. ICP waveform analysis offers granular information on compensatory reserve and cerebral autoregulation. Noninvasive methods, such as cranial micro-deformation sensors and transcranial Doppler-derived parameters offer accessible bedside assessment. These tools, alongside others such as optic nerve sheath ultrasound and pupillometry, facilitate earlier detection of decompensation, guide individualized therapy and improve prognostication.

Keywords
intracranial compliance, intracranial pressure, neurocritical care, neuromonitoring

INTRODUCTION

Traumatic brain injury (TBI) and other acute brain insults, such as subarachnoid hemorrhage (SAH) and hydrocephalus, represent significant global health challenges, contributing substantially to morbidity and mortality in critical care settings [1]. Central to the pathophysiology of secondary brain injury in these conditions is the intricate interplay of intracranial volumes and pressure, governed by the concept of intracranial compliance (ICC). ICC reflects the brain's capacity to accommodate changes in intracranial volume [e.g. due to edema, hematoma, or cerebrospinal fluid (CSF) accumulation] without a disproportionate rise in intracranial pressure (ICP) [2]. A high ICC indicates a robust buffering capacity, whereas reduced ICC signifies a precarious state where even minor volume additions can lead to precipitous ICP elevations and potentially catastrophic brain herniation [3].

[a]Division of Neurosurgery, Department of Neurology, University of São Paulo Medical School, Brazil, [b]Department of Biomedical Engineering, Faculty of Fundamental Problems of Technology, Wrocław University of Science and Technology, Poland, [c]Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy and [d]Department of Anesthesia and intensive care, Neuro Critical Care, University Hospital of Clermont Ferrand, France

Correspondence to Sérgio Brasil, MD, PhD, University of Sao Paulo: Universidade de Sao Paulo, São Paulo, Brazil.
E-mail: sbrasil@alumni.usp.br

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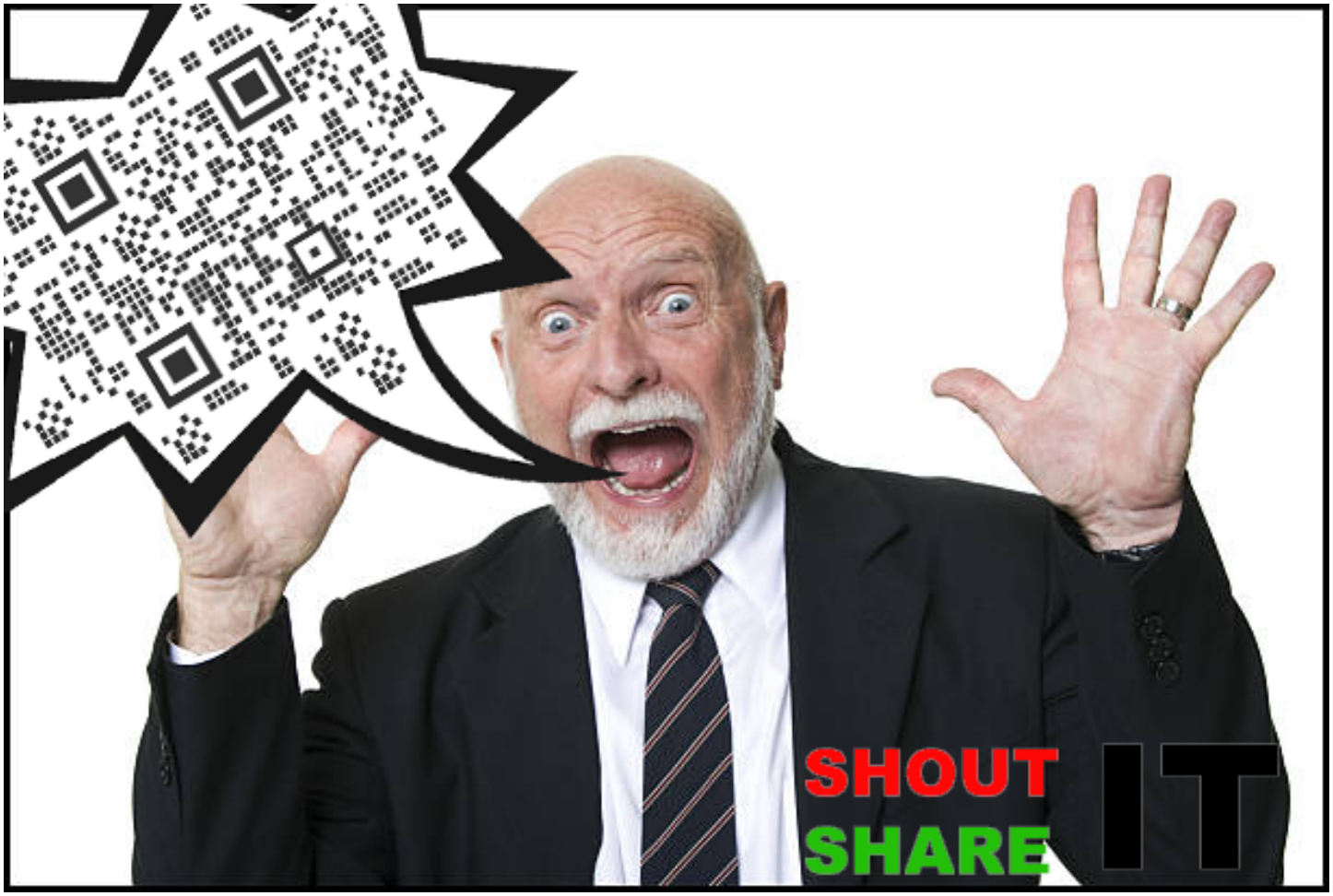
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KEY POINTS

- Modern acute brain injury management is shifting from static intracranial pressure thresholds to dynamic, continuous assessment of intracranial compliance.
- New research extends the classical Monro-Kellie doctrine, integrating the glymphatic system and parenchymal shrinkage as crucial dynamic components of intracranial compliance.
- Advanced neuromonitoring techniques with ability to ICP waveform analysis offer real-time data on cerebral compensatory reserve.
- Dynamic intracranial compliance assessment enables early detection of decompensation and personalized therapies, moving away from a reactive, threshold-based approach.
- Integrating new concepts and advanced monitoring tools promises to optimize therapeutic strategies, improve prognostication, and ultimately enhance outcomes for patients with acute brain injury.

Historically, the management of intracranial hypertension has largely revolved around monitoring absolute ICP values and intervening when predefined thresholds are exceeded [4,5]. While this approach has reduced mortality, it often provides a delayed and incomplete picture of the underlying intracranial dynamics. The recognition that ICP is merely a symptom of underlying compliance changes, rather than a direct measure of compensatory reserve, has spurred a paradigm shift in neurocritical care [6,7▪▪]. Although the ICP dose has also been suggested as a better indicator of morbidity [8]. There is a growing consensus that a more nuanced, continuous, and dynamic assessment of ICC is essential for truly individualized patient management and improved outcomes [7,9–12▪▪].

This review aims to provide an updated perspective on ICC, encompassing recent advances in its pathophysiology, the evolution of monitoring techniques and their emerging clinical implications. We will delve into how new insights into CSF dynamics, coupled with sophisticated invasive and noninvasive monitoring tools, are redefining our understanding and management of ICC, moving towards a more proactive and personalized approach in neurocritical care.

THE EVOLVING UNDERSTANDING OF INTRACRANIAL COMPLIANCE: PATHOPHYSIOLOGY

The foundational understanding of ICC stems from the Monro-Kellie doctrine, which posits that the cranial vault is a rigid box containing three main components: brain parenchyma, CSF, and blood. A change in the volume of one component must be offset by an equal and opposite change in another, or ICP will rise [13]. While this doctrine provides a crucial conceptual framework, modern neuroscience recognizes that intracranial dynamics are far more complex and fluid than a simple static volume relationship [6,7,14–17▪▪].

The pressure–volume curve, first extensively characterized by Marmarou and others, illustrates the nonlinear relationship between intracranial volume and pressure [18–20]. Initially, when compensatory reserves are intact, large volume additions result in minimal ICP changes (high compliance). As compensatory mechanisms (e.g. CSF displacement, venous blood outflow and neurons shrinkage) are exhausted, the curve becomes steeper, meaning small volume changes lead to significant ICP increases (low compliance) [21]. The amplitude–pressure index (RAP) has become a cornerstone in quantifying this dynamic relationship invasively. RAP represents the correlation coefficient between mean ICP and the amplitude of the ICP pulse waveform (ICPw). A RAP close to zero indicates adequate compliance, while a RAP approaching +1 signifies impaired compliance, reflecting the brain's diminishing ability to buffer volume changes [22,23]. After the critical ICP threshold is exceeded – such as the rightward bending of the pressure–volume (*P–V*) curve, compliance is reduced and RAP falls below 0 (negative correlation). A positive correlation between tomographic patterns of brain swelling and the RAP index has further solidified its clinical utility in assessing the buffering reserve [24].

Beyond the traditional components, emerging research highlights the critical role of the glymphatic system in maintaining intracranial homeostasis and influencing compliance. Eide *et al.* [25] elucidated the importance of this brain-wide waste clearance system, which facilitates the perivascular exchange of CSF and interstitial fluid. Interstitial fluid is directly secreted into the CSF spaces from interstitial compartments [26,27]. The exact proportion of CSF originating from interstitial spaces remains unclear, but evidence from animal studies suggests that this contribution is significant and participates in the removal of metabolic byproducts [27,28]. Impairment of glymphatic function, as observed in conditions like idiopathic intracranial hypertension, can lead to CSF stagnation and altered brain water content, thereby directly impacting ICC [29].

Similar mechanisms have been proposed to explain the occurrence of external hydrocephalus following TBI. External hydrocephalus involves the impairment of extra-axial CSF flow, leading to an enlargement of the subarachnoid space. This condition

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is associated with reduced ICC, higher ICP, and altered CSF dynamics, but without ventriculomegaly [30]. The impairment of CSF resorption after a brain injury, exacerbated by SAH, may be facilitated by postural positioning after TBI (30° head elevation maximum), as this positioning decreases the pressure gradient between the CSF spaces and the promotes a significant adjustment of the spinal epidural space [31].

This introduces a 'new concept' of compliance, where the efficiency of CSF clearance pathways, beyond simple production and absorption, becomes a dynamic factor in the brain's compensatory capacity. The interplay between arterial pulsations, CSF flow and glymphatic transport suggests a more integrated view of intracranial dynamics, where vascular health directly influences CSF clearance and, consequently, ICC. These factors were considered in the updated Monro-Kellie doctrine 4.0 [7▪▪].

Additional elements contribute to cerebral compensatory reserve [15]. In a retrospective study of 96 intracerebral hemorrhage patients, using serial CT scans (~23 h apart), it was observed a significant reduction in contralateral hemisphere volume by approximately 12.7 ml ($P < 0.0001$), independent of midline shift or hematoma growth. These findings suggest that parenchymal shrinkage may serve as an active compliance mechanism in humans. This shrinkage likely reflects tissue-level changes such as cell contraction and higher packing density in regions remote from the hemorrhage, which may help buffer ICP rise beyond standard compensatory pathways.

ADVANCED MONITORING OF INTRACRANIAL COMPLIANCE

The shift towards dynamic ICC assessment necessitates sophisticated monitoring tools capable of capturing real-time physiological changes. Both invasive and noninvasive techniques have evolved significantly, offering complementary insights.

Intracranial pressure waveform analysis

While invasive ICP monitoring remains the gold standard for direct pressure measurement, its true value extends beyond absolute numerical values to the detailed analysis of the ICP waveform (ICPw). The ICPw typically comprises three characteristic peaks: P1 (percussion wave), P2 (tidal wave), and P3 (dicrotic wave) [19]. The P2 peak, classically described as a tidal wave or a reflection wave, coincides with a maximum volume in the cerebral arteries [32,33]. The morphology of this pulse wave provides critical information about ICC. The relative amplitude of the second peak (P2) to the first peak (P1) is a well established indicator of ICC. As ICC deteriorates, P2 tends to increase relative to P1, leading to a P2/P1 ratio greater than 1 [34]. Similarly, the time-to-peak (TTP), representing the time from the start of the pulse to its highest amplitude, also reflects changes in intracranial volume and compliance [35,36].

More recently, advanced algorithms and machine learning approaches have enabled the derivation of new metrics from the ICPw. The algorithm known as Morphological Clustering and Analysis of Intracranial Pressure (MOCAIP) evaluates various pulse shape metrics, including peak height, latency, and curvature, using a complex peak identification technique [37]. MOCAIP-derived metrics have been shown to be useful in various clinical scenarios, including the prediction of ICP elevation [37]; however, accurate peak identification remains a methodological challenge due to waveform variability caused by inter-patient differences, pathological changes, and noise or artifacts in the signal. In contrast, the Pulse Shape Index (PSI) classifies entire ICP pulse wave morphology into four categories that represent incremental states of compliance [38,39]. PSI variations can precede subsequent ICP insults, suggesting its potential for early warning [40,41]. Combining both metrics, AmpICP, which reflects acute volume compensatory changes influenced by mean ICP, and PSI, which also captures age-related stiffening of the cerebrovascular system, may provide a more comprehensive assessment of cerebrospinal volume-pressure compensation [42].

NONINVASIVE APPROACHES

The limitations of invasive monitoring (e.g. infection risk, invasiveness, cost, accessibility) have driven the development of noninvasive methods for ICC assessment.

Transcranial Doppler-derived indices

Transcranial Doppler (TCD), a noninvasive tool for assessing cerebral blood velocity, can also provide indirect insights into ICC. The pulsatility index, is the TCD most studied parameter in this regard. It is given by the formula:

Sv-Dv/Mv

Where: Sv – systolic cerebral blood flow velocity, Dv – diastolic cerebral blood flow velocity, Mv – mean cerebral blood flow velocity.

The ability of pulsatility index to discriminate intracranial hypertension remains uncertain, as this parameter may be influenced by various systemic variables or conditions, including CO_2 levels, dehydration, sepsis, aortic valve failure, barbiturate use, and aging [43]. Mathematical modelling indicates that pulsatility index results from the combined effects of cerebral perfusion pressure, arterial pulse

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amplitude, cerebrovascular resistance, arterial bed compliance and heart rate [44]. The pulsatile-apparent resistance (PaR) was a pulsatility index formula improvement, considering the arterial pressure systolic and diastolic differences, therefore, reducing confounding factors and outperforming the pulsatility index in intracranial hypertension detection [43]. Additional advanced TCD-derived parameters, including cerebral arterial blood volume (CaBV), critical closing pressure (CrCP), and resistance × area product (RAp) vary following ICP fluctuations, reflecting alterations in cerebral hemodynamics after ICC deterioration [23,24]. Assessing CrCP and ICP synchronous increases, it is understood that the brain mechanisms to preserve blood flow are much scarcer in front of ICP than for ABP, what challenges the binomial CPP = ABP – ICP [45,46].

Cranial micro-deformation sensor (B4C system)

The B4C system represents a significant advancement in noninvasive ICPw monitoring. This wearable sensor detects micrometric pulsatile cranial expansions, which accurately reproduce the ICPw [36]. It was validated against invasive ICP monitoring, demonstrating a strong correlation between B4C-derived parameters (P2/P1 ratio, TTP, PAx and PSI) and their homologous invasively measured [47–50]. This system offers the potential for continuous, accessible bedside monitoring, moving ICP assessment towards a vital sign status [7▪▪].

Further studies by means of different strategies assessed either ICC or cerebrovascular autoregulation (CAR) using this technique. Two studies used CaBV, thus combining TCD and B4C, to demonstrate that changes in the P2/P1 ratio reliably correspond to increased intracranial resistance [33,49]. Another study explored P2/P1 ratio and TTP behaviors following the RAP index variations (neutral, positive, and negative), the first describing a ceiling effect for these parameters. It means that P2/P1 ratio and TTP values may begin to decrease when reaching the point of critical ICP, following the RAP index, which becomes negative [51]. Finally, to assess CAR, a high correlation was observed from moving windows of ICP and B4C pulses amplitudes with arterial blood pressure (ABP) variations [52]. Such index is named PAx and warrants further studies due to its similarity with the well known pressure-reactivity index (PRx), deeply investigated on the optimal CPP framework [10,53].

Nonpulsatile techniques

Other techniques that do not monitor intracranial pulsatile phenomena may serve as sources of surrogate information about ICC. Optic nerve sheath diameter ultrasound (ONSD) and automated pupillometry have been extensively studied and applied in clinical settings. TCD, automated pupillometry, and ONSD are included in the B-ICONIC consensus, which provides global expert recommendations for noninvasive monitoring when invasive ICP methods are not possible or advised [54].

ONSD is a quick and simple way to rule out intracranial hypertension. The optic nerve, covered by meninges after leaving the retina, directly reflects subarachnoid ICP changes. Clinicians measure ONSD using a linear probe, positioning the cursor 3 mm from the retina. Multiple studies and three meta-analyses have shown ONSD can help detect elevated ICP, although study results vary widely [55]. In addition to predicting intracranial hypertension and mortality, the ratio between the ONSD and the dimension of the eyeball was also found to be effective [56]. Although the ONSD clearly correlates with ICP, the threshold evocative for intracranial hypertension significantly varies between 5 and 6.8 mm [57]. In a clinical setting, values below 5 mm can reasonably discard intracranial hypertension while values above 6 mm call for further examinations and rapid treatment [58]. A simple formula (nICP = 5 × ONSD – 14) allows close ICP estimation, which gets even more accurate when combined with the straight sinus blood velocity (SSv) obtained through the occipital window (nICP = 4,23 × ONSD + 0,14 × SSv – 14,51) [59].

Automated pupillometry measures pupil response to light, providing size, constriction velocity, and an index (NPi) based on several parameters. Intracranial hypertension may compress the mesencephalon, impairing pupil reaction. A systematic review found eight articles on the subject, all stating an inverse correlation between NPi and ICP [60]. NPi power on intracranial hypertension discrimination is not high, but it provides objective prognostic information in critically ill brain injury patients and may aid in dynamic risk stratification and monitoring.

While still in earlier stages of validation for ICC, other noninvasive techniques exploring cerebral bioimpedance [61], photoplethysmography [62], optic sensors [63] and the measurement of tympanic membrane displacement [64,65] recently demonstrated to have potential to be used in the future in clinical settings.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The integration of new pathophysiological concepts and advanced monitoring techniques is profoundly impacting the clinical management of neurocritical patients. Duration and intensity of ICP surges, known

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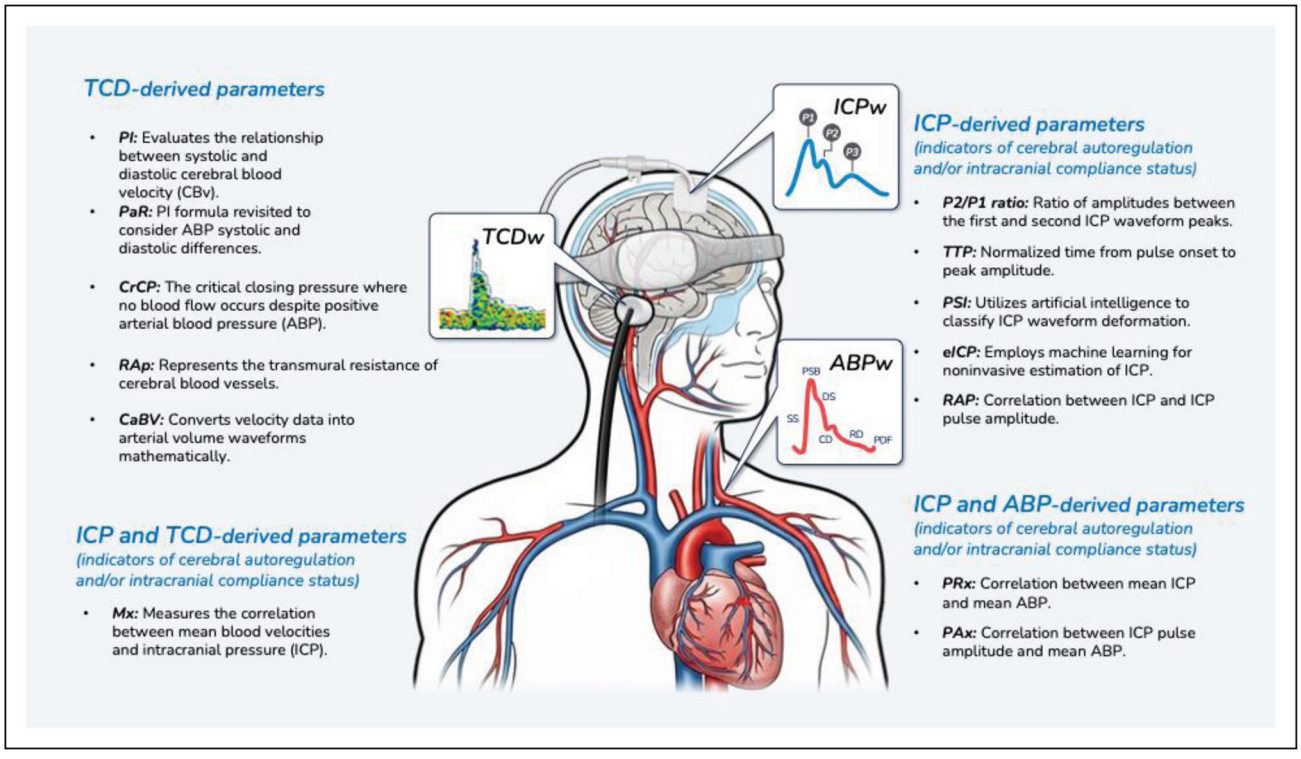
TCD-derived parameters
PI: Evaluates the relationship between systolic and diastolic cerebral blood velocity (CBv).
PaR: PI formula revisited to consider ABP systolic and diastolic differences.
CrCP: The critical closing pressure where no blood flow occurs despite positive arterial blood pressure (ABP).
RAp: Represents the transmural resistance of cerebral blood vessels.
CaBV: Converts velocity data into arterial volume waveforms mathematically.
ICP and TCD-derived parameters
(indicators of cerebral autoregulation and/or intracranial compliance status)
Mx: Measures the correlation between mean blood velocities and intracranial pressure (ICP).
TCDw
ICPw
P1
P2
P3
ABPw
PSB
DS
SS
CD
RD
PDF
ICP-derived parameters
(indicators of cerebral autoregulation and/or intracranial compliance status)
P2/P1 ratio: Ratio of amplitudes between the first and second ICP waveform peaks.
TTP: Normalized time from pulse onset to peak amplitude.
PSI: Utilizes artificial intelligence to classify ICP waveform deformation.
eICP: Employs machine learning for noninvasive estimation of ICP.
RAP: Correlation between ICP and ICP pulse amplitude.
ICP and ABP-derived parameters
(indicators of cerebral autoregulation and/or intracranial compliance status)
PRx: Correlation between mean ICP and mean ABP.
PAx: Correlation between ICP pulse amplitude and mean ABP.

FIGURE 1. A concise overview of several extensively studied indexes and parameters obtained from pulsatile waveforms. ABP, arterial blood pressure; CaBV, cerebral arterial blood volume; CrCP, critical closing pressure; eICP, estimated ICP; ICP, intracranial pressure; ICPw, intracranial pressure waveform; Mx, mean velocities-ICP index; PaR, pulsatile apparent resistance; PAx, pressure-amplitude index; PI, pulsatility index; PRx, pressure-reactivity index; PSI, pulse-shape index; RAP, pressure-amplitude correlation; RAp, resistance/area product; TCD, transcranial Doppler; TTP, time-to-peak.

as 'ICP dose' [66] suggest that fixed ICP thresholds may not be universally applicable and support an approach based on individualized ICP management. Therefore, dynamic ICC parameters, such as RAP, P2/P1, TTP, NPi, ONSD and PSI, provide real-time feedback on the brain's compensatory reserve, potentially allowing clinicians to tailor therapies to the patient's specific physiological state [67]. For instance, a patient with a 'normal' ICP but severely impaired compliance (e.g. positive RAP, elevated P2/P1 or PSI) may warrant more aggressive care and/or intervention than a patient with transiently elevated ICP but intact compliance.

The ability of advanced waveform analysis (e.g. PSI and P2/P1) to reflect changes in compliance before a significant rise in mean ICP offers a crucial window for early intervention [37,41,68]. This early warning potential can facilitate proactive management strategies, potentially preventing irreversible secondary brain injury [40,68]. Beyond real-time monitoring, ICC parameters hold significant prognostic value. CAR and compliance indices were associated with patient outcomes in TBI [22,24,69,70]. This information can aid in prognostication and guide the intensity and type of therapeutic interventions, from osmotic agents to CSF diversion or surgical decompression [7▪▪,71]. Furthermore, integrating noninvasive tools into routine clinical practice, particularly in resource-limited settings, offers a significant opportunity to democratize advanced neuromonitoring [72]. Figure 1 outlines bedside and research indexes and parameters for identifying cerebrovascular physiology.

LIMITATIONS

Despite these advancements, challenges remain. The widespread adoption of these sophisticated monitoring techniques requires robust validation in larger, multicenter trials. Each technique has limitations, requiring clinicians to interpret results carefully to avoid being misled. Standardization of measurement protocols and interpretation is also crucial. Developing a universal monitoring protocol is challenging due to the considerable differences among health services and locations. The increasing volume and complexity of neuromonitoring data necessitate the development of advanced analytical tools, including machine learning and artificial intelligence, to extract meaningful clinical insights.

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CONCLUSION

The field of ICC is undergoing a profound transformation. Moving beyond the classical understanding of the Monro-Kellie doctrine, new concepts are providing a more comprehensive view of intracranial dynamics. Simultaneously, advancements in both invasive and noninvasive monitoring technologies are enabling real-time, dynamic assessment of the brain's compensatory reserve. The ability to continuously monitor parameters like the RAP index, P2/P1 ratio, TTP, and PSI, and to integrate insights from noninvasive tools like the B4C system and TCD, empowers clinicians to move away from reactive, threshold-based management towards proactive, individualized neurocritical care. While further research and validation are essential, these new concepts and monitoring capabilities hold immense promise for optimizing therapeutic strategies, improving prognostication, and ultimately enhancing outcomes for patients with acute brain injury.

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Conflicts of interest

Dr. Sérgio Brasil is a senior scientific advisor for Brain4-care. The other authors declare no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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